A Multicenter Clinical Trial using NGI Technology
National Library of Medicine Contract N01-LM-9-3537

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Reverse Site Visit - National Library of Medicine
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X-linked Adrenoleukodystrophy

- Affects nervous system white matter, adrenal cortex and testis.

- Childhood cerebral, adult spastic paraparesis and "Addison only" forms often co-occur in same family.

- Accumulation of saturated very long chain fatty acids (VLCFA) fue to impaired function of peroxisomal VLCFA Coenzyme A ligase.

- Xq28 gene codes for peroxisomal membrane protein that is part of ATP Binding Cassette transporter

X-ALD Phenotypes and their Relative Frequency

1. Cerebral (35-40%)
    Diffuse inflammatory demyelination, rapid progression.
    Childhood form (onset 4-8 years) most common
2. Adrenomyeloneuropathy (AMN) (40-45%)
    Distal axonopathy mainly in spinal cord.
    Paraparesis in young adults, progress over decades
3. Addison Disease only (20-30% at onset)
    Most develop AMN later

Phenotypes frequently co-occur in same family
>50% of heterozygous women develop AMN in middle age or later

MINIMUM FREQUENCY OF X-ALD IN THE UNITED STATES

	Male Population	Female Population	Total Population
Hemizygotes (a)	1:21,000	1:42,000	
Heterozygotes (b) (calculated)		1:14,000	1:28,000
Hemizygotes + Heterozygotes			**1:16,800**

(a) Similar results in France and Canada

(b) 60% of heterozygotes develop symptoms in middle age or later

Childhood Cerebral Form of X-linked Adrenoleukodystrophy

- 35% of total X-ALD population
- Onset before 10 years: earliest 2.75 years: peak: 7 years
- Initial symptoms resemble attention deficit-hyperactivity
- May respond to ritalin
- Progression to apparent vegetative state 1.9 =/- 2 Years
- Range 0.5 to 10.5
- Adrenal insufficiency 85% (often biochemical only)
- MRI abnormality preceed clinical findings
- 65% parieto-occipital; 15% frontal; 15% projection fibers; 5% atypical

October 28, 1983

Thomas

May we wait here?

She says she's fine

Well read five lines,

I've saved nine dies
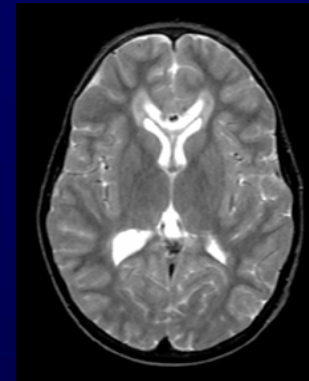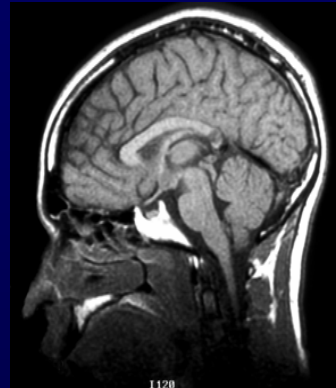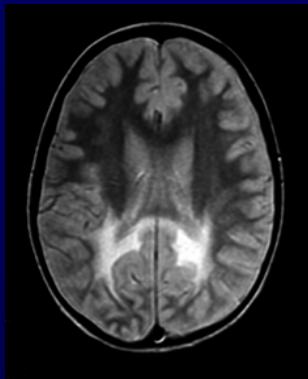
Dave sneezes.

January 13, 1984

Thomas

the

the river

Li es

N

Scoring System For MRI Abnormalities In X-linked Adrenoleukodystrophy

parietal occipital white matter	4	auditory pathway	4
anterior temporal white matter	4	projection fibers	2
frontal white matter	4	cerebellum	2
corpus callosum	5	basal ganglia	1
visual pathway	4	atrophy	4

- 34 point scale
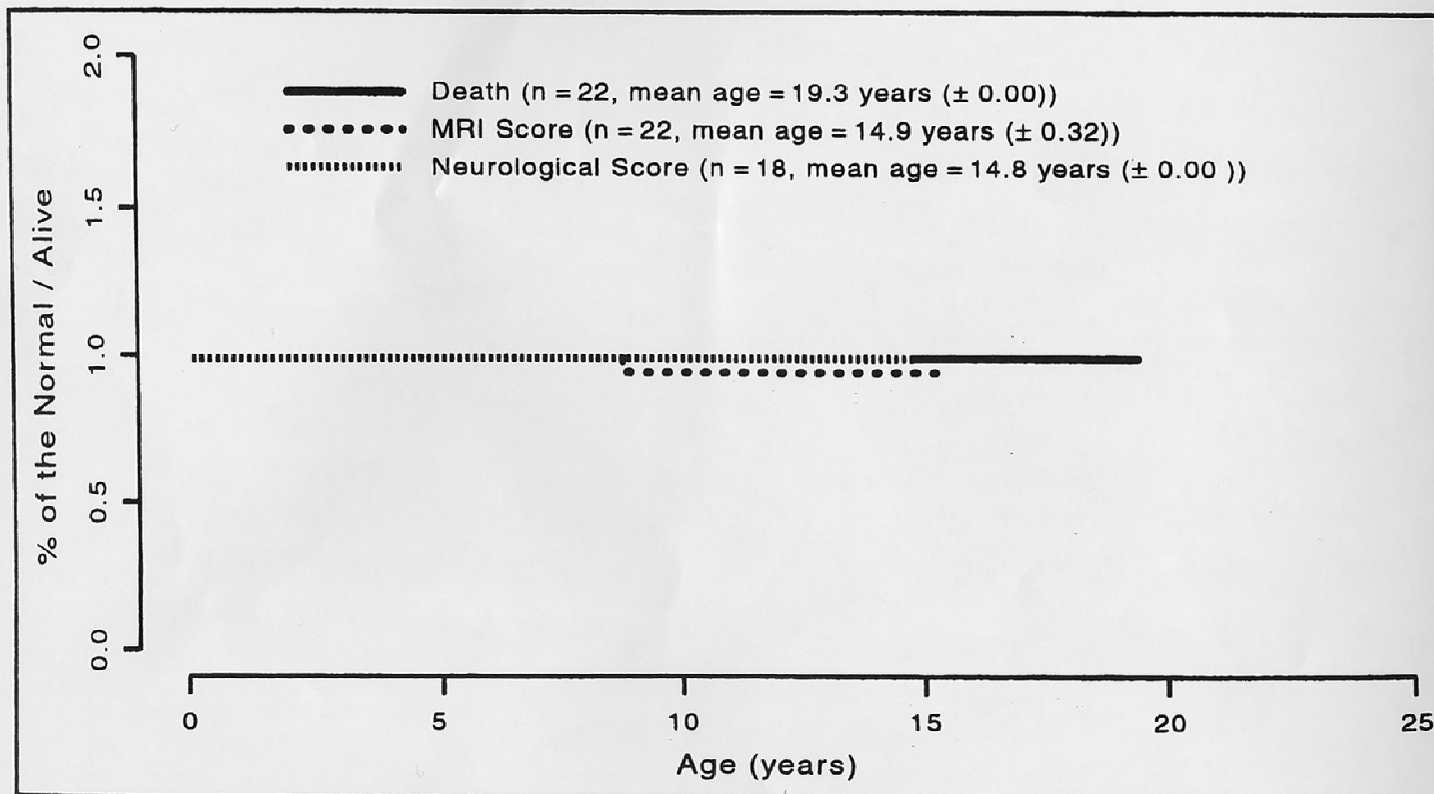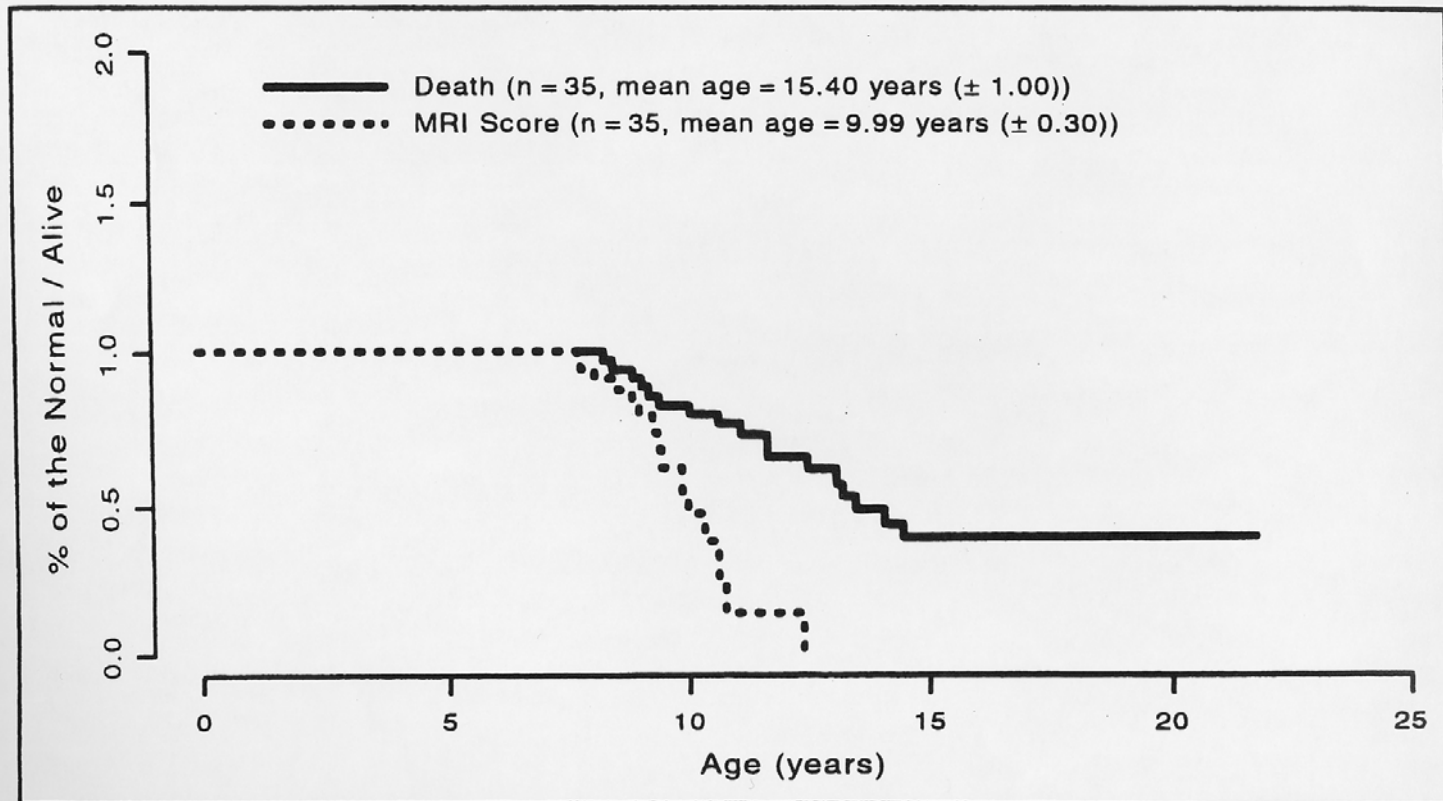- score ≥ 1 abnormal

Baseline Age > 7 and ≤ 10 Years Old
Baseline MRI Score <1

MRI Score (Loes) increased by at least 2 points
Neurological Score (Raymond) increased by at least 1 point

Death (n = 22, mean age = 19.3 years (± 0.00))
MRI Score (n = 22, mean age = 14.9 years (± 0.32))
Neurological Score (n = 18, mean age = 14.8 years (± 0.00))

Baseline Age > 7 and ≤ 10 Years Old
Baseline MRI Score ≥ 3

MRI Score (Loes) increased by at least 2 points

Legend:
- Death (n = 35, mean age = 15.40 years (± 1.00))
- MRI Score (n = 35, mean age = 9.99 years (± 0.30))

Y-axis: % of the Normal / Alive
X-axis: Age (years)

Predictive Power of Neuroimaging

- Combination of Loes Score, pattern of MRI lesions and presence or absence of gadolinium contrast predict disease progression with a probability of up to 95%. (Loes et al. Neurology 2003)

- MR Spectroscopic Imaging further increases the predictive power (Eichler et al. Neurology 2002)

- New MR applications such as Diffusion Tensor Imaging and Magnetization Transfer are being evaluated and may play a major role in the near future.

ALD MRI network
National Library of Medicine Contract N01-LM-9-3537

- To create an Internet-based infrastructure that will allow MRI images to be transmitted to and retrieved from a central database

- To understand the impact of the network on collaboration – what are we doing here – how and who

- To understand the privacy and security aspects of the network

Results
ALD MRI Network

- 30 sites contacted

- 19 participating
  - 14 contributing sites
  - 2 contributing/reviewing sites
  - 3 review only

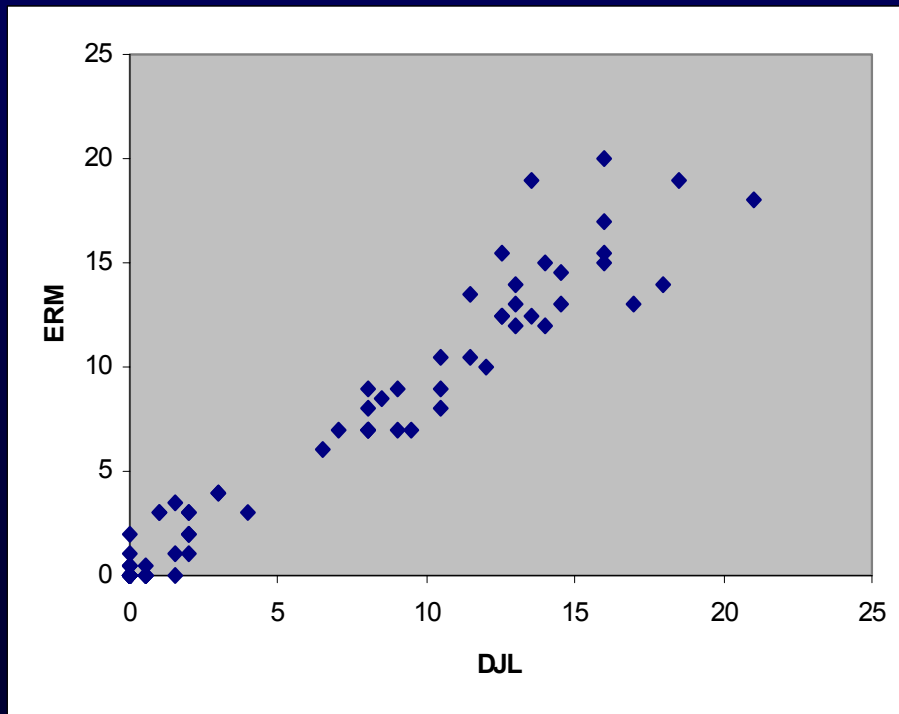- 126 patients, 231 exams, 46461 images (May 2000 – June 2003)

Results
NGI experience

- NGI used by 1 site for DICOM transmission (Fairview)

- Timing studies indicate four fold increase in performance of NGI vs Internet

- NGI cost exceeds $12,000 per month

Interobserver Reliability

- **87 MRI studies of X-ALD patients**
- **Scored by two Neuroradiologists: D.J.L. & E.R.M.**

Correlation
  overall : 97.5%
  MRI score $\leq$ 3: 98.5%
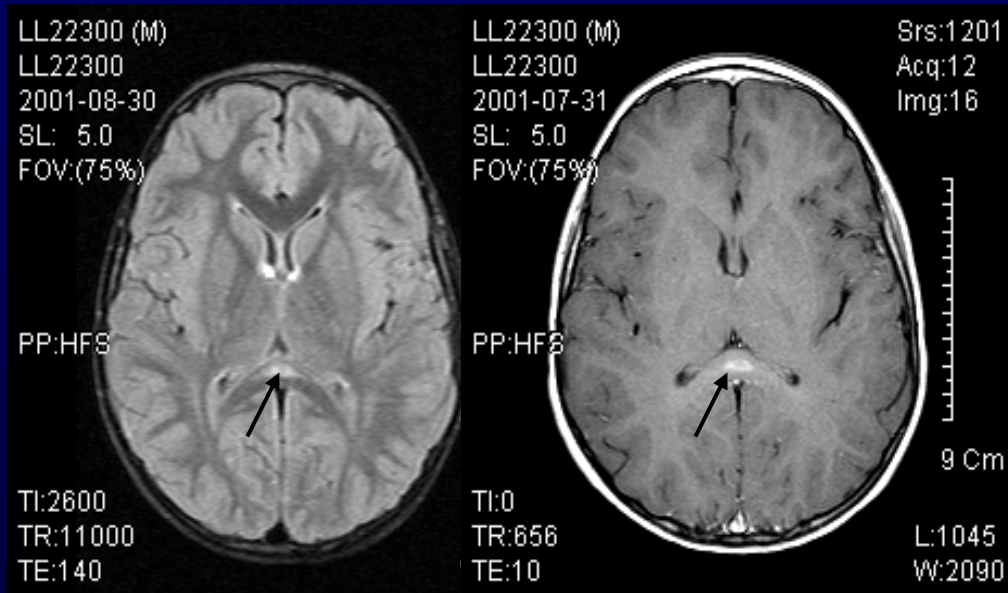 MRI score > 3: 87.2%

MRI Network
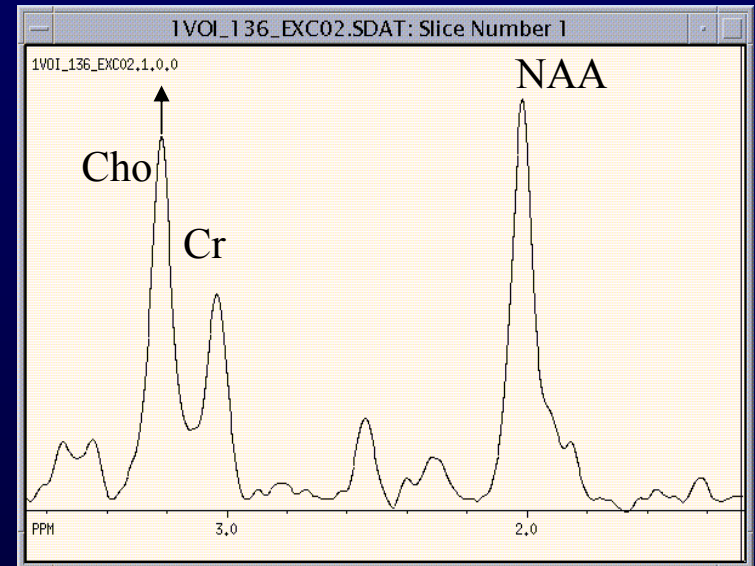# Evaluation of Bone marrow Transplant

- Ongoing study

- Assessment of MRI Outcome in transplanted X-ALD patients

- Data from Fairview Hospital vs. historical data at KKI

- Use of the network for the transmission of MRIs to KKI

MR Transmission Clinical Case

Loes score 1, contrast positive

Voxel adjacent to lesion, high Choline

→ Bone marrow transplantation indicated but since lesion in early stage procedure postponed until a good match was found

MR Transmission
Clinical Case

- 7 year old patient with X-ALD
- Clinically Asymptomatic
- MRI and MRS in Houston's Children Hospital (8/31/2001) reported to be abnormal

Question if bone marrow transplant indicated?

- MRI sent with DICOM server PiView
- MRI scored by three different physicians

- MRS raw files sent to KKI
- Spectra processed by MRS expert at KKI

GRANT 1RO1 HD39276 - 01A2

"Multicenter Therapeutic Trials in X-linked Adrenoleukodystrophy"

Award to Kennedy Krieger Institute

September 2002-2007

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Conclusions

- MRI network has established the basis for a multi-center clinical trial in ALD

- NGI allows Real-time evaluation of MRI

- New powerful MR applications will require capacity of NGI

File size for new MR methods

Type of MR technique	size of a study in Megabytes
Conventional MRI in DICOM	10
MR Spectroscopic Imaging	20
Global Magnetization Transfer Imaging	92
Diffusion Tensor Imaging	690

DTI

MRSI

DICOM

GMT
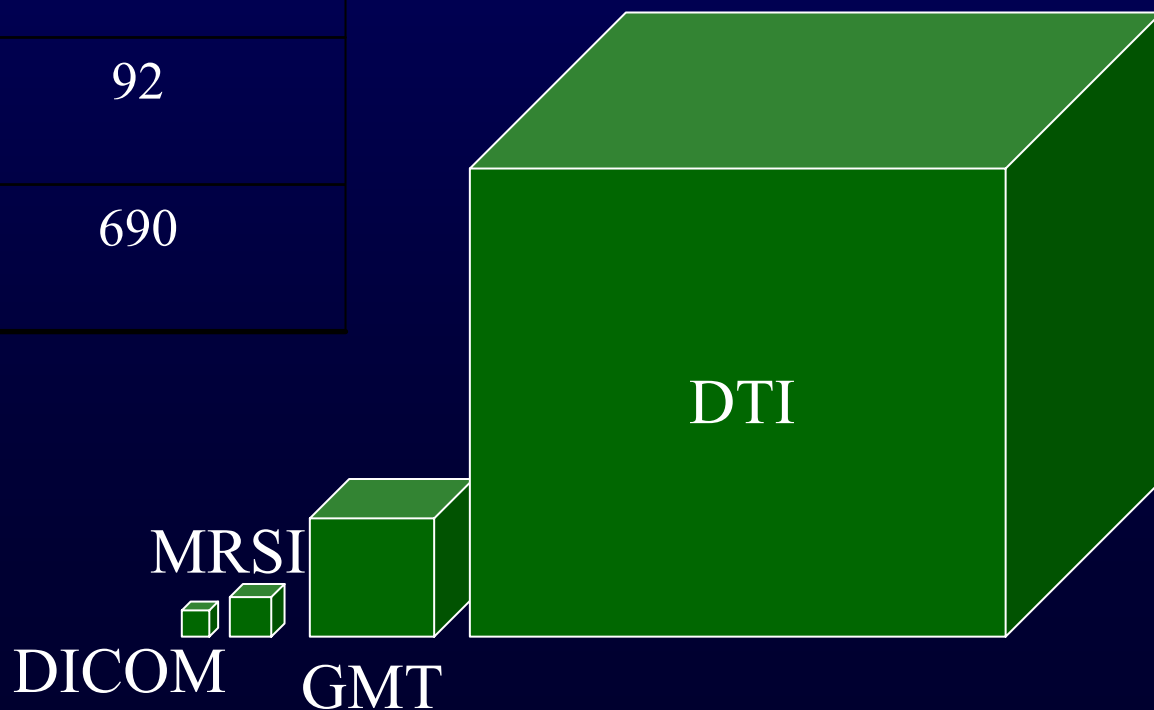
Discussion SLIDES

Contrast-enhanced MRI

Number of Patients	Enhancement (-)	Enhancement (+)	Total
No Progression	20	2	22
Progression	2	19	21
Total	22	21	43
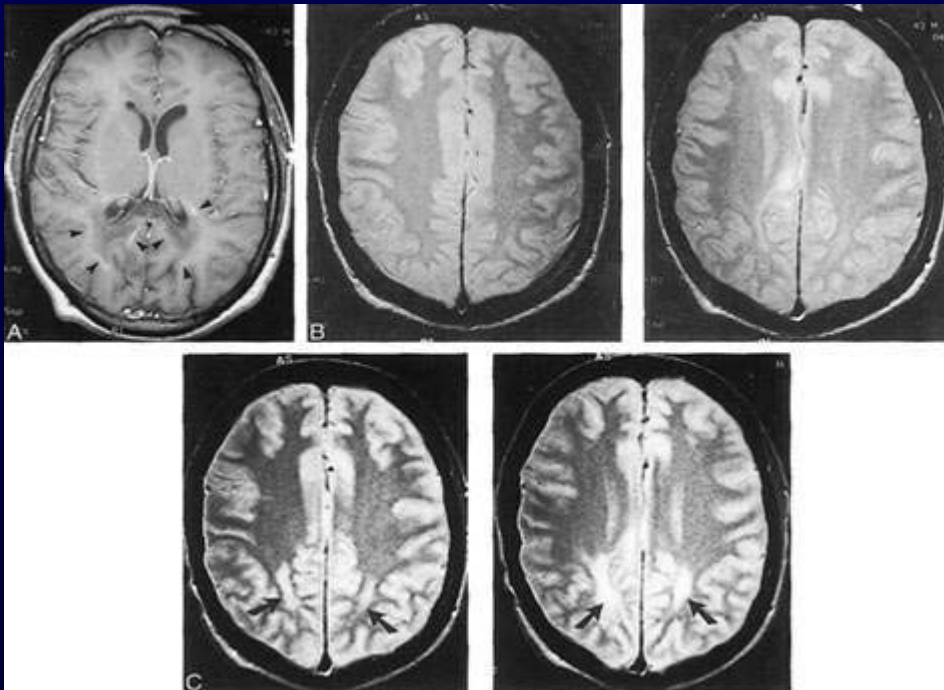
sensitivity: 90%
Pos. pred. value: 90%

Melhem ER et al
(Am J Neuroradiol 2000)

Prediction of MRI progression in cerebral X-ALD

- **Pattern 1**   **($r^2 = 0.96$)**

  predicted MRI follow-up score after one year =

  2.28 enhancement – 0.07 initial age + 1.05 initial MRI score + 0.87

  (contrast pos. defined as 1, contrast neg. defined as 0)

- **Pattern 2**   **($r^2 = 0.79$)**

  predicted MRI score after 1 year =

  2.1 initial MRI score – 4.4 age subgroup – 0.48

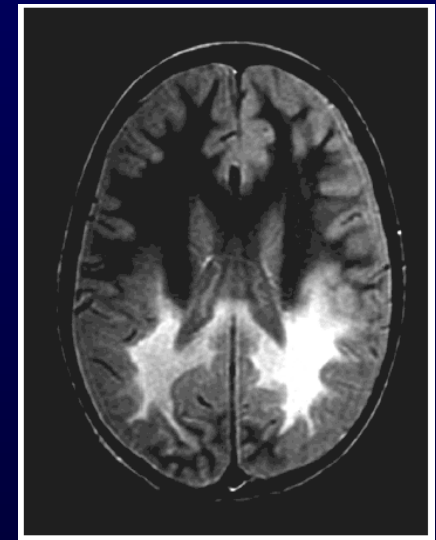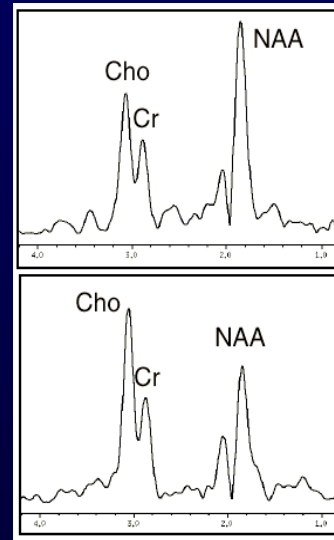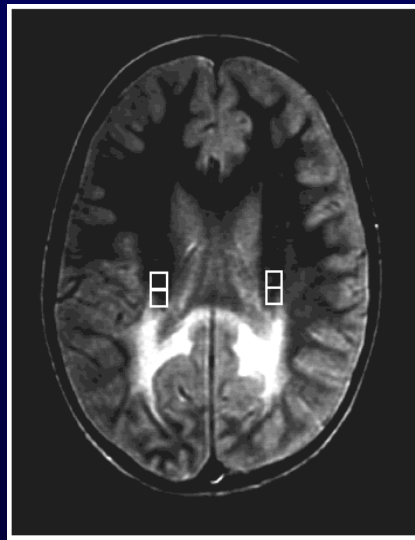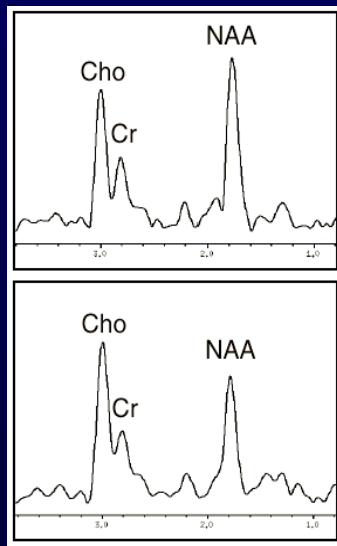 (age subgroups: 0: <13 years, and 1: ≥13 years old)

- **Pattern 3**

  – no significant effect of initial MRI score or age

  – of the 20 patients only 1 case had an increase of 10.5 over 6.9 years and 2 developed cerebral symptoms

  – the average MRI progression is 0.42 Loes scores per year

Loes, Fatemi, et al., Neurology 2003

MRSI as a Predictor for Disease Progression

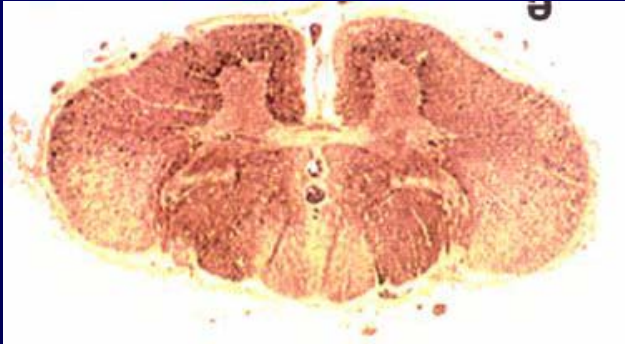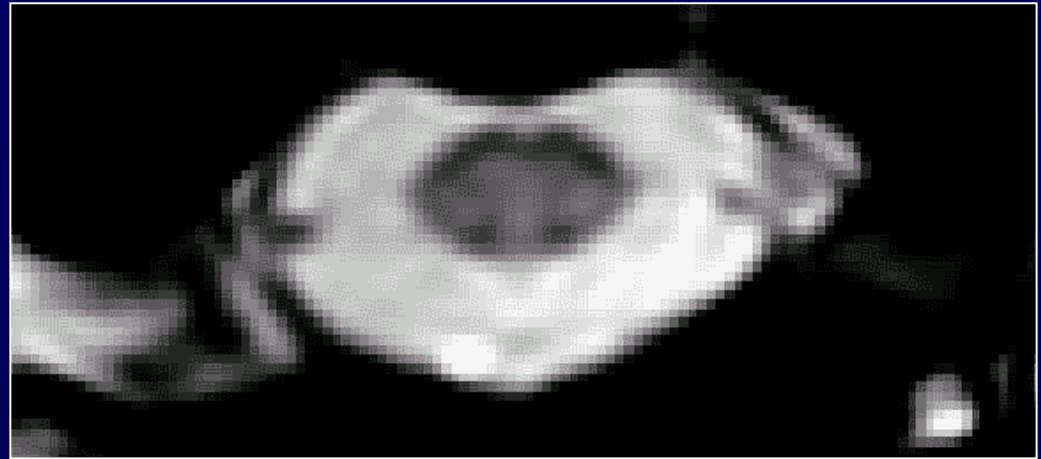**Feb 1995**   **May 1995**

Reduced NAA/Choline ratio predictive for disease progression

Eichler F, Barker PB et al. , Neurology 2002

Global Magnetization Transfer MRI

Powers J, et al.

Journal of Neuropathology and Experimental Neurology, 2000, 59: 89-102
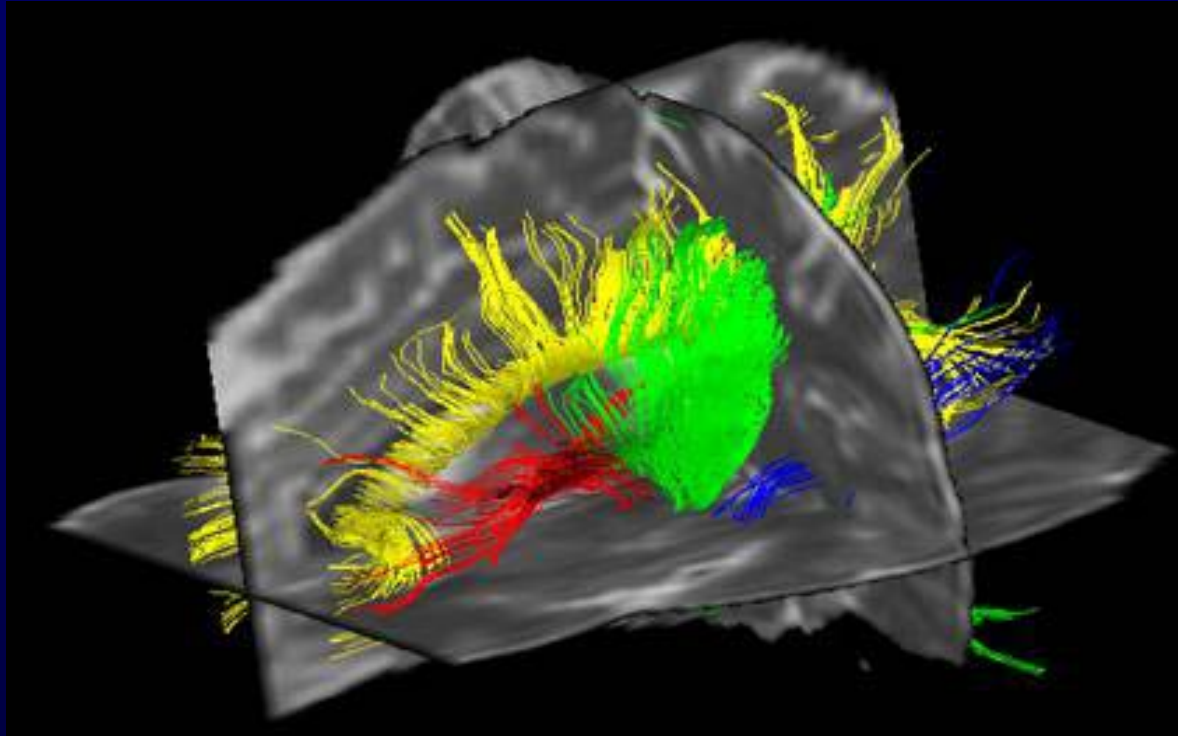

AMN Patient 1

AMN Patient 2

Diffusion Tensor MRI (DTI)

- Tracking of axonal fibers
- Allows quantitative assessment of specific tracts (e.g. corticospinal tract)
- May serve as a marker in Adrenomyeloneuropathy

Remote Software Processing of MRI data

Remote site (e.g. MGH)

DTI raw Files

690 Mega Bytes

Interactive tool for 3D fiber tracking

Central Computer at KKI

DTI expert at KKI can access data from remote site and analyze the data in real time